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The Carcinogenicity of Chromium

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The carcinogenicity of chromium compounds is reviewed with specific attention to the gaps in knowledge for risk estimation and research needs. The most important problems at present are whether trivalent chromium compounds cause cancer, and whether there is a difference in cancer causing effects between the soluble and the slightly soluble hexavalent compounds in the practical exposure situation. Dose estimates for risk estimation based on epidemiological investigations are also lacking.

Present evidence indicates that the trivalent chromium compounds do not cause cancer although high concentrations in some *in vitro* systems have shown genetic toxicity. Hexavalent chromium compounds cause cancer in humans, in experimental animals and exert genetic toxicity in bacteria and in mammalian cells *in vitro*. Epidemiological evidence and animal experiments indicate that the slightly soluble hexavalent salts are the most potent carcinogens, but proper identification and characterization of exposure patterns in epidemiological work are lacking. Workers also tend to have mixed exposures. Soluble and slightly soluble salts are equally potent genotoxic agents *in vitro*.

Further work for establishing dose estimates for risk evaluation in epidemiological work is important. *In vitro* systems should be applied for further identification of the mechanism of the carcinogenic effects, and animal experiments are urgent for comparison of the carcinogenic potency of the different hexavalent salts. Hexavalent chromium salts must be regarded as established carcinogens, and proper action should be taken in all industries with regard to such exposure. At present the carcinogenic risk to the general population caused by chromium compounds seems to be negligible, chromium in cigarettes, however, is an uncertainty in this respect. The amount of chromium and the type of chromium compounds inhaled from cigarettes is not known.

The general toxicology of chromium compounds has been reviewed by the National Academy of Sciences (*1*) and by the National Institute of Occupational Safety and Health (*2*). The carcinogenic properties of chromium compounds have been specifically reviewed by the International Agency for Research on Cancer (*3*). More recently, several condensed reviews of the toxicology of chromium have been published (*4-8*), and possible mechanisms of the carcinogenic effect have been reviewed based on recent developments in *in vitro* tests (*9-11*).

This paper does not present an extensive historical review of the carcinogenicity of chromium. Some results which are important for discussing the present gaps in knowledge of the carcinogenic effects of chromium are presented. The most important problems at present are whether trivalent chromium causes cancer, and whether there are differences in cancer causing effects between soluble and slightly soluble salts of hexavalent chromium. The specific compound or compunds which have caused cancer in chromate workers are not known, and an important problem is also the lack of adequate dose registration for dose-response evaluations and risk estimation. The importance of smoking in chromium carcinogenesis is not known.

Chemistry-Biological Interactions

Chromium is a transition metal with an atomic weight of 52. The most common valences are 0, +2, +3, and +6. The only important chromium ore is chromite, $FeOCr_2O_3$. Chromates are produced by a smelting, roasting and extraction process. Soda ash or soda ash and lime are reacted with chromite. With the soda ash method, sodium chromite is formed, and this substance is subsequently oxidized to sodium chromate and extracted. The lime method forms calcium chromate/chromite complexes which

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are insoluble in water but soluble in acid. The residue from both processes contains an unknown mixture of mostly insoluble chromium compounds (*12*). In the ferroalloy industry and for refractory work, chromites are used, and only limited amounts of hexavalent chromium compounds are assumed to be present. Chromium metal is produced from chromates by reduction.

Both trivalent and hexavalent chromium are found in nature, but the trivalent is the more common form. Divalent chromium compounds will oxidize unless protected from air. Chromium in biological materials is probably always trivalent (*13*). When animals are exposed to hexavalent chromium, the hexavalent form exists for some time indicated by a different distribution pattern than after exposure to the trivalent form (*4*). After some time only trivalent chromium is found. When added to tissue *in vitro*, the reduction takes place within minutes (*14*). The so-called glucose tolerance factor, which has not been fully identified, is a trivalent chromium complex with niacin (*15*). The trivalent chromium ion has a strong tendency to form coordination complexes and chelates in aqueous solutions and does not exist in the free form (Table 1). Water may serve as a ligand, but in complex solutions water may be replaced by other anion (halides, sulfates, organic acids). Under alkaline conditions, forming of polynucleate complexes which may precipitate due to a replacement of water with OH^- takes place (*13*).

The hexavalent form of chromium is almost always linked to oxygen and is a strong oxidizing agent (Table 1). The hexavalent form is readily reduced to the trivalent form by contact with organic matter. Oxidation of trivalent chromium (or chromium metal) to the hexavalent form in organic matter seems unlikely (*13*).

Hexavalent chromium readily passes the cell membrane while the trivalent form does not seem to have this property (*13, 16*). Once in the cell, the hexavalent form is reduced to the trivalent. The site in the cell for this conversion has been suggested to be both the plasma membrane, the endoplasmic reticulum, the mitochondria or the cell nucleus (*17-20*). The biological effects of the hexavalent form may thus either be related to the reduction process, to the subsequent binding of the trivalent chromium to macromolecules, or possibly to both. Trivalent chromium complexes with a number of ligands within the cell. High concentration of chromium is normally found in nucleic acids (*21*). Its function, if any, is not known, but a stabilizing effect of chromium on RNA has been demonstrated *in vitro* (*22*). Chromium in RNA may be in an organic form; organochromium in compounds of toxicological significance has not been described, but chromium carbonyl causes cancer in a transplantation animal technique (*23*).

Environmental Exposure

Chromium exposure to the general public has important health consequences because of its skin sensitizing effect. Chromium is among the most common sensitizers in allergic eczema (*24*). The daily intake from food has been estimated to be in the range of 0.03-0.1 mg (*1, 4*). The chromium content in municipal drinking water has been estimated to be in the same range as in rivers and lakes (1-10 μmg/l.), occasionally somewhat higher (*1*). Urban air concentrations have been reported from less than 10 ng/m^3 to about 50 ng/m^3, for rural stations seldom above 10 ng/m^3 (*1*). A possible source of chromium exposure to the general public is waste dumps for chromate-producing plants

Table 1. Identity and solubility of some chromium compounds.[a]

Compound	Formula	Valence	Aqueous solubiity
Chromium	Cr	0	Insoluble
Chromium acetate	$Cr(COOCH_3)_3 \cdot H_2O$	3	Soluble
Chromium carbonate	$Cr_2O_3 \cdot CO_2 \cdot 4H_2O$	3	Slightly soluble
Chromium phosphate	$CrPO_4$	3	Insoluble
Chromic oxide	Cr_2O_3	3	Insoluble
Calcium chromate	$CaCrO_4$	6	Slightly soluble
Chromium trioxide (chromic acid)	CrO_3	6	Soluble
Lead chromate	$PbCrO_4$	6	Insoluble
Potassium dichromate	$K_2Cr_2O_7$	6	Soluble
Potassium chromate	K_2CrO_4	6	Soluble
Sodium dichromate	$Na_2Cr_2O_7$	6	Soluble
Sodium chromate	Na_2CrO_4	6	Soluble
Barium chromate	$BaCrO_4$	6	Insoluble
Strontium chromate	$SrCrO_4$	6	Insoluble
Zinc chromate hydroxide	$Zn_2CrO_4(OH)_2 \cdot H_2O$	6	Slightly soluble

causing local air or water pollution (*12*).

Tobacco has been reported to contain up to about 30 mg/kg of chromium, but most values are reported to be low 5 mg/kg (*25*). No estimates of the inhaled amount or of the chemical form of chromium in tobacco smoke have been found. With the possible exception of chromium in tobacco, where further investigations are needed, no association has yet been made between chromium exposure to the general public and human cancer.

Occupational Exposure

Potentially hazardous exposure to chromium compounds may take place in the metal refining/chromate production industry, in the metallurgic industry and in the refractory brick industry. Hazardous chromium exposure is also reported in industries which are secondary users of chromium chemicals in pigments production and plating. Welders and grinders in the secondary metal industry (steel welding and grinding, anticorrosive paints) are also exposed to chromium compounds, and chromium may be found in small amounts in a variety of industrial settings (catalysts in chemical industry, paint production and use). Chromium is extensively used in tanning (*2*).

Mancuso and Hueper (*26*) and Mancuso (*27*) reported exposure levels of up to 1 mg/m^3 in a chromate producing plant, but most values were in the range of 0.26-0.52 mg/m^3. A five-shift mean value of 1.35 mg/m^3 for a sack filling operation was reported by Langard and Norseth (*28*) in an old chromate pigment plant, while in another modern plant levels were mostly below 0.2 mg/m^3. In a ferrochromium plant most average shift values (personal sampling) were below 0.05 mg/m^3, but occasional values up to 1.3 mg/m^3 (total chromium) were recorded (*29*). In a recent review a chromium exposure up to 5 mg/m^3 in the plating industry was mentioned, but most values were in the range 0.1-0.2 mg/m^3 (*2*). Similar values for chromium exposure in different industries have been indicated in a review by Hayes (*30*). The exposure levels seem to have been fairly constant during the last 20 years in older plants, but lower values are found in new plants.

Epidemiological Studies

The epidemiology of cancer in chromium exposed workers has recently been reviewed by Hayes (*30*). Even if the first cases of cancer were described in secondary users of chromates (*30*), the most extensive epidemiological results stem from the chromate producing industry. An increased risk of respiratory cancer in this industry has been irrefutably established from a number of countries. In a review paper from 1950, Baetjer (*31*) described 109 cases of cancer in the chromate producing industry, 11 cases in the chrome pigment industry and 2 cases in other industries. Already in 1936 German health authorities recognized lung cancer as a possible occupational disease associated with chromate dust exposure. Other papers reviewing the number of cases in different countries have also appeared (*6*, *32-34*). Most cases have been reported from the chromate production industry, but also reports from the chrome pigment industry have appeared (*28*, *35*).

Hueper (*36*) reviewed the histological classification of 123 cases of lung cancer in chromate workers and found 46 squamous cell carcinomas, 66 anaplastic types and 11 adenocarcinomas. Great variations have been reported for the period from the first exposure to chromates and the diagnosis of cancer (*6*). A time period as long as 47 years has been found, mean value from different authors seems to be about 20 years with observed to expected ratios of up to about 40. Cancer of the nasal cavities has been reported in chromate workers, as well as laryngeal cancer (*6*).

Mancuso (*27*) and Mancuso and Hueper (*26*) stated in 1951 that inhalation of chromite ore dust characterized as insoluble chromium might be an important factor in the production of lung tumors. None of their lung cancer deaths were found in workers exposed predominantly to soluble chromium compounds (hexavalent). Mancuso (*37*) recently published a followup of this group and stated that both exposure to trivalent and hexavalent chromium constitute a cancer risk. The original group was divided into workers exposed to predominantly insoluble or soluble compounds. Mancuso found that the lung cancer death rates increased by a gradient level of exposure both to insoluble and to total chromium. None of the groups had exclusive exposure to either type of compund. There is no information about a possible gradient exposure to soluble (hexavalent) compounds in the group exposed mainly to insoluble compounds. Nor is there information about a gradient exposure to insoluble, nor to slightly soluble hexavalent compounds in either group. The similar increased risk in both groups as estimated from the death rates may indicate that such exposure is reasonable. If not, trivalent chromium should be an equally potent carcinogen as are the hexavalent compounds.

In a report by the United States Public Health Service the exposure pattern for 10 cases of lung cancer based on weighted average exposures by job classification has been reported (*30*). A low risk was

contributed to chromite exposure and to exposure to soluble compounds. It was concluded that exposure to acid-soluble, water-insoluble compounds in the roast and residue constituted the excess risk. Most epidemiological reports contain no classification of exposed workers to specific jobs or exposure patterns, but in a recent paper, Hayes (*38*) indicates that the high risk is related to the "wet" part of the process where mainly water soluble hexavalent compounds are handled. The author states, however, that most workers had not been exclusively employed in a single part of the plant.

The major secondary use of chromium is in chromate pigment production, in the plating industry and for tanning. Gross and Kölsch in 1943 (*39*) reported 8 cases from the pigment-producing industry, and Baetjer (*31*) reported 11 cases, but some of the latter had been reported before. An increased risk of respiratory cancer was demonstrated by Langard and Norseth (*28*) (risk ratio 38) in a pigment-producing plant, but the risk estimate was only based on three cases. Assuming a Poisson distribution, the increased risk is, however, significant at the 0.05 level. The workers were exposed to lead and zinc chromate at levels up to 1.35 mg/m^3 as chromium. In a survey of U.S. pigment plants (*40*), an increased risk was found for workers exposed to both zinc and lead chromate, and a corresponding increased risk was found for workers with exposure classified as high for lead and zinc chromates by Davies (*35*). Maltoni (*41*) has reported 21 cases of lung carcinoma in a group of 200 chromium pigment workers. Cytological examinations were performed on a group of 116 workers and the incidence of abnormal cells (class III-VI Papanicolaou) was about 25% as compared to 6% in the PVC industry, 1.6% in the chemical industry in general, and 0.6% in heavy smokers.

Of specific interest for the evaluation of soluble versus insoluble, or slightly soluble, chromate compounds as cancer causing agents is the cancer risk in the plating industry because of the uniform exposure to soluble compounds. Royle (*40, 41*) compared a population of platers exposed to chromium (VI) oxide to a reference population matched with respect to age, sex and smoking habits. He analyzed 246 certified causes of death and found a higher number of malignancies than expected for lung and pleura, for gastrointestinal tract and for other unspecified sites, but only total deaths from malignant neoplastic disease were significantly increased (51 compared to 24 expected, significant at the 1% level). Waterhouse (*43*) in a preliminary communication, found total deaths from malignant disease above expected number in a population of chromium platers, but the difference was not statistically significant. He found, however, 49 deaths from lung cancer among male employees compared to 34.88 expected ($p < 0.05$). The significance of these reports is uncertain. Okuba and Tuschiya (*44*) have reported the results from an epidemiological study of 589 plating firms in Japan. No increased risk for respiratory cancer was found, but the conclusions are uncertain because of short observation time and a high loss (10%) to follow up. If exposure to hexavalent chromium in the plating industry constitutes a cancer risk, the risk is certainly much less than in the chromate producing or in the chrome pigment industry with the exposure levels which have been prevailing in these industries for the last 20 years.

No epidemiological investigations have been published for the large group of chrome pigment users in various other industries, but based on experience from pigment production, these workers must be regarded as being at risk if there is a significant exposure. A large group with a possible risk is welders and grinders exposed to welding aerosols from stainless steel or from working with chromate primed materials. With stainless steel welding, about 70% of the total chromium in the aerosol is in the hexavalent form as soluble sodium or potassium monochromates (*45*), and fume particles have been shown to be mutagenic (*46*). Both the relative amount of hexavalent and the solubility of these salts seem, however, to vary with the type of welding (*47, 48*). Exposure levels for total chromium up to 1 mg/m^3 as chromium have been reported for welders (*47, 49, 51*). In a recent epidemiological investigation of workers in a ferrochromium plant Langard (*29*) reported a suspect increase of respiratory cancer. Cancer incidence among 976 workers employed before 1960 and employed in ferrochromium or ferrosilicon production was investigated. Nine cases of lung cancer were found in the total population, seven in the subpopulation of 325 employed in ferrochromium production. The expected number of respiratory cancers was 3.1 and 1.8 using national and local expected incidence rates, respectively, and less than 1 compared to an internal reference population. Dust concentrations (total chromium) of up to 1.3 mg/m^3, were recorded at the time of the survey, from 11 to 33% were water-soluble components. Axelson (*50*) could not demonstrate an increased risk of respiratory cancer in a corresponding investigation, but the industrial process in this case did not produce significant amounts of hexavalent chromium compounds (soluble). Pokrovskaya (*49*) reported increased incidence of respiratory cancer in workers employed in ferrochromium production. Also other carcinogens were, however, present [benzo(a)pyrene, hexavalent chro-

mium]. Only one inconclusive report has been published from the refractory brick industry (*30*). No reports have been found from the tanning industry.

The possibility that exposure to chromium compounds might cause cancer at other sites than in the respiratory tract is a matter of discussion. Based on five cases of cancer observed in a small group of chromate workers, Teleky (*52*) suggested a relationship between exposure to chromates and cancer in the gastrointestinal tract. Taylor (*53*) reported gastrointestinal cancer cases to be slightly in excess in a similar group. In the survey of 3 U.S. chromate pigment plants, an increased risk of gastric cancer was found in one plant (*54*). A slight increase in the number of cancers in the gastrointestinal tract has also been reported in chromium electroplaters (*40,42*). Langard and Norseth (*55*), in a followup of the previously reported cohort from a pigment plant found three cases of gastrointestinal cancer in a small subpopulation of 24 workers with more than three years of employment by the end of 1972. The numbers are too small for final conclusions. Also in the ferrochromiun plant referred to previously, a suggested increase risk of gastrointestinal cancer was found. Among the 325 ferrochromium workers in the survey, five cases of gastric cancer were reported compared to 3.18 expected (*29*).

Animal Experiments

A review of animal data up to 1972 has been published by the International Agency for Research on Cancer (*3*). The results support the assumption that the most potent carcinogenic chromium compounds are the slightly soluble hexavalent salts, specifically calcium chromate. This compound is carcinogenic by tracheal instillation, and by intramuscular and intrapleural injection. Calcium chromate is the only chromium compound which has given respiratory cancer after inhalation in animal experiments (*56*), although tests in progress with suggested positive results have been reported for unspecified intermediates from chromate production (*30*). Instillation experiments with soluble chromates have given negative results, and the same is reported for inhalation experiments with such compounds (*3*).

Using the tracheal implantation technique of Laskin (*57, 57*), Levi (*59*) demonstrated a carcinogenic effect of calcium chromates. Also zinc chromate gave positive results. One cancer was reported in a group of 100 rats exposed to chromic acid compared to 8 with calcium chromate and 3 with zinc chromate. The chromic acid results should therefore be regarded with some caution. Implantation of chromic chromate alone did not give any cancers, but after the dispersion of the same substance in silica, three cancers were found. No explanation is given for this result. Intermediates from chromate production have also been shown to be carcinogenic in tracheal implantation and possibly as mentioned after inhalation (*30, 60*). The specific active agent cannot be identified in the latter experiments.

In Vitro Studies

Important recent developments in the understanding of chromium carcinogenicity have come from the study of mutagenic activity in bacteria and from work with isolated cell systems. Metals as mutagens have recently been reviewed by Flessel (*10*), and Sunderman (*11*) has reviewed the effect of metals on genetic material both in isolated biochemical systems, in microbiological systems and in *in vitro* cell systems.

Chromates are mutagenic in *Escherichia coli* and in *Salmonella typhimurium* (*60-72*) and influence DNA repair in *Bacillus subtilis* (*69, 73*). Venitt and Levi (*60*) and Petrilli and de Flora (*62*) in a comparative study found no significant differences in dose-response between the soluble and slightly soluble compounds in either the Salmonella or the Coli system. Chromates seem to be directly acting mutagens as no activation by microsome fractions is necessary. De Flora (*19*), on the contrary, found a deactivation of sodium dichromate as a mutagen in the Salmonella system by adding liver microsomal fraction. This has been confirmed by Löfroth (*18*) and Petrilli and de Flora (*67*). Nishioka (*73*) found that the mutagenic effect disappeared when the hexavalent salts were reduced to the trivalent form in the experimental system using sodium sulfite. Oxidation of the trivalent form to the hexavalent in the test system, on the other hand, increases the activity (*68*). Trivalent chromium salts seem in general to be without or with a very weak mutagenic activity in bacterial systems.

Of particular interest is a theory set forward by Löfroth (*18*) that the causative agent in chromium mutagenesis is trivalent chromium bound to genetic material after reduction of the hexavalent form by a NADPH dependent microsomal enzyme system. The decrease in activity reported by the reduction of the hexavalent form to the trivalent form (*19, 66, 73*), might then be explained by a decreased uptake of the trivalent form by the cells.

Potassium dichromate is mutagenic in yeast (*74*), and soluble hexavalent salts induce morphological transformation and chromosomal aberrations in mammalian cells *in vitro* (*69, 75-81*). Chromosomal aberrations are also found in workers engaged in

chrome production (*82*). Nakamuro et al. (*69*) found that both hexavalent and trivalent soluble salts had this effect, but the hexavalent salts were the most potent. Newbold et al. (*79*) could not, however, demonstrate effects of lead chromate (insoluble hexavalent). Soluble trivalent salts had no such effect (*79*, *80*). In hamster embryonic cells the effect of potassium dichromate disappeared when chromium was reduced to the trivalent form in the experimental system (*77*). Sirover and Loeb (*83*) found increased error frequency in DNA synthesis *in vitro* with both trivalent and hexavalent chromium with a 30% error with chromium concentrations of 0.64 *mM* (trivalent) and 16*mM* (hexavalent). These results support the trivalent form to be the active agent at the site of action. Trivalent chromium salts have also been shown to give positive results in other experimental model systems by altering the physiochemical properties of macromolecules (*84-87*).

Various chromium compounds may influence the metabolism of genetic materials (*88-93*). Levis et al. (*88-91*) claim, based on studies of DNA/RNA synthesis in hamster fibroblasts (BHK line) and human epithelial-like cells (HEp line), that the hexavalent form is reduced by passing the plasma membrane, but assume that trivalent chromium is the active agent within the cell. Both the soluble hexavalent and trivalent salts decreased the DNA synthesis, but after adding either form only the trivalent was found inside the cells. The necessary concentration was a 100 times higher for the trivalent form than for the hexavalent form to get an effect. Hexavalent chromium first stimulated nucleoside uptake by the cells, then inhibited the uptake; amino acid uptake was only inhibited. The trivalent form had no such effects (*91*, *92*). Also an effect of potassium dichromate on mitosis in mammalian cells has been demonstrated (*93*).

Evaluation of Present State of Knowledge

Chromium as the glucose tolerance factor has an essential function in humans. High concentration of chromium is found in RNA and a stabilizing function of chromium has been suggested. Only the hexavalent and the trivalent chromium compounds have biological importance. The hexavalent form is a strong oxidizing agent and is almost always found together with oxygen. The hexavalent form is rapidly transformed to the trivalent form in contact with organic materials. Hexavalent chromium salts readily pass biological membranes, trivalent chromium does not seem to do so. Once in the cell, the hexavalent form is rapidly reduced to the trivalent form. The biological effects of chromium, including the carcinogenic effect are results of this transformation, subsequent binding of the trivalent form to ligands within the cell or both. The trivalent form has a strong tendency to form coordination complexes and chelates in aqueous solutions, it may precipitate at physiological pH because of polynucleate complex formation with OH^- ions.

An increased risk of respiratory cancer has been irrefutably established for workers in the chromate industry. A corresponding risk has been shown in the chromate pigment producing industry. An increased risk of respiratory cancer has not been conclusively established in ferrochromium production, in the refractory brick industry or in the plating industry. Secondary users of chromate pigments, including welders and grinders, must be regarded as being at risk on theoretical grounds, but epidemiologically an increased risk of cancer has never been shown. The number of epidemiological investigations are, however, limited for all groups except for workers in the chromate producing industry. An increased risk of cancer at other sites than the respiratory tract (gastrointestinal tract) has been suggested, but not finally established.

Negative results from the plating industry indicate that soluble chromates either do not cause cancer or are less potent carcinogens than slightly soluble compounds (calcium chromate). Based on results from the chromate producing industry is it not possible to either verify or dismiss this theory because of insufficiently described exposure patterns. Because of analytical procedures, slightly soluble compounds seem mostly to be regarded as trivalent. This may not be correct as also slightly soluble hexavalent salts may be present in the working environment (calcium–zinc–lead chromates).

Animal experiments support the assumption that the slightly soluble hexavalent salts (calcium chromate) are the active agents, but inhalation experiments are few. Tracheal instillation experiments are, however, highly suggestive that this is the case. Soluble and slightly soluble hexavalent salts (calcium chromate) are equally potent for causing mutations in bacterial systems, and both soluble and slightly soluble salts cause chromosomal damage or cell transformation in isolated cells. Trivalent chromium may cause mutation and cellular transformation *in vitro* in high concentrations. The differences in activity of the soluble and slightly soluble hexavalent salts in the practical exposure situation may be related to retention time on the mucous membrane in the respiratory tract, to a time/concentration factor caused by slow solubilization and removal, or to differences in the intracellular

kinetics of the two different classes of compunds.

There is at present no epidemiological evidnece for trivalent chromium to be carcinogenic. Epidemiological evidence is supported by animal experiments and particularly by *in vitro* results and biochemical considerations. When tested in systems which require that chromium passes biological membranes to exert an effect, reduction of the hexavalent form to the trivalent reduces or abolishes the effect. Similarly, trivalent chromium which is without effects in such systems when oxidized to the hexavalent form in the system has genotoxic effects. The trivalent form has a more potent genotoxic effect than the hexavalent in systems without biological membranes, and as the hexavalent form is rapidly reduced in contact with biological material, the active substance at the site of action is probably the trivalent form. There is no agreement as to in what part of the cell this reduction takes place, probably at several sites. It is neither known to what extent the effects caused by hexavalent chromium are directly related to the reduction process or to the subsequent binding of the trivalent form. Available evidence indicates, however, that the mechanism of chromium carcinogenicity involves a direct interaction of trivalent chromium with genetic material or genetic processes, though indirect interaction by virus or other chemical substances has been suggested (*95-97*).

No risk estimation of cancer in workers exposed to chromium in the chromate producing industry based on reliable dose-response information is possible at present. Some exposure data have been recorded, but the chemical characterization of data in the very complex exposure situation in the chromate producing industry is insufficient. A complicating factor is that most workers have probably had more than one job. It should, however, be noted that even if there are relatively few investigations reported from the plating industry, refractory brick industry and ferrochromium industry, the risk of cancer must have been less than in the chromate producing industry and in the chrome pigment industry with the exposure levels which have been prevailing for the last 20 years. Levels for exposure and risk cannot, however, be established.

Gaps in Knowledge and Research Needs

Chromium carcinogenesis is in good accordance with the somatic mutation theory for cancer, but why and how the mutant cell develops into a cancer is, as for other chemical carcinogens, not known. Once this has been mentioned, the most important gaps in our knoweldge are data for risk estimation based on dose-response for specified industrial processes or for specific chromium compounds.

This problem calls for research with model systems and for further epidemiological research. Further studies on the mechanism of the carcinogenic action is necessary for the evaluation of the interrelationship between the trivalent and hexavalent form in carcinogenesis. It is not known if trivalent chromium might penetrate the biological membrane under specific circumstances. Animal experiments with defined chemical compounds of chromium are urgently needed. Specifically the relationship between soluble and slightly soluble compunds should be evaluated in such systems. This problem is difficult to solve in epidemiological investigations because of the mixed exposures in many industries. Inhalation or intratracheal instillation should be the preferred methods.

Further epidemiological investigations should be started in all populations where exposure to chromium takes place. Not only cancer in the respiratory tract should be looked for, a possible increased incidence of cancer in all organ systems should be investigated. Cancer in the gastrointestinal tract may be of particular interest. This is also the case for exposure to trivalent chromium. Mixed exposure with smoking is an important problem in risk estimation. The amount of chromium inhaled from cigarettes, and the chemical form are not known.

At present we have recorded an increased number of workers with cancer in some high risk groups. It is unrealistic to assume that low risk groups may be evaluated in a similar way. For low risk estimation both in epidemiological work and when using experimental animals, the necessary number of individuals under study soon becomes prohibitive.

Extrapolation from high exposure in relatively small groups for short time periods to low level, long-time exposure in large groups for a disease like cancer is hazardous.

Recent developments in applying model systems for mutagenicity studies are promising for evaluation of the mechanisms of cancer caused by metals. Furthermore, epidemiologic studies should be refined with a more detailed work history for the exposed groups. This is difficult for retrospective studies, especially for metal carcinogenesis. Care should be taken to record relevant dose-indicators for prospective and for retrospective work. International collaboration in epidemiological work should be encouraged to increase the size of the exposed groups, and registration of workers and exposure levels should be introduced in industry as recom-

mended by ILO (*98*). Epidemiological follow-up of the benefits of early diagnosis is important. Early diagnosis must, however, not be sold as a cure for industrial cancer.

Lastly, let us not forget that even if there are definite gaps in our knowledge in chromium toxicology, our knowledge is sufficient for us to work for an improvement of the working conditions where excessive and unnecessary exposure to chromium takes place in our industry, or in the general environment. Thus, epidemiological investigations as recommended are not necessary for proving that some chromium compounds cause cancer, but they are needed for estimating a maximum risk based on inevitable exposure of populations at hand.

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